salt from the column. Following rinsing, the nucleic acids can be eluted from the column using a compatible non-toxic aqueous unbuffered organic solvent nucleic acid being concentrated in a desalted solution. The desalted solution can then be easily lyophilized to yield the pure, desalted nucleic acid in a dried form.

The claimed methods are distinct from claiming the purification process itself, as implied in the Office Action at page 3, last line through page 4, line 1. The advantage to the protocol of the present invention lies not in the method of purification *per se*, but in the advantage the use of material conveys on the subsequent steps of concentrating and desalting of the nucleic acids.

The conventional methods currently used in the art for desalting and concentrating nucleic acids are not efficient, and involve the use of volatile organic buffers to elute the nucleic acids from the columns in the purification process. The method of the present invention avoids the use of volatile buffers, significantly reducing the time necessary to complete the procedure as compared to existing methods of reverse phase capture. Moreover, the present invention allows the use of safer chemicals to elute the nucleic acid from the column.

Although the elements used in the invention are indeed commercially available, others skilled in the art have not used these available elements to achieve the claimed method, despite a great need in the art for a faster, safer and cleaner methods of desalting and concentrating oligonucletides and/or monomers. In fact, a talk given at the IBC 2nd Annual Conference on Oligonucleotide Technologies (October 26-28, 1998, in San Diego), a prominent scientist in the art specifically pointed out a need for better desalting and concentration methodolgies (see attached abstract and table from talk). The methods of the current invention circumvent the limitations found with reverse phase capture and other available methods, and thus represent a significant advance over methods currently used in the field.

The method of the invention can be applied to almost any scale of operation. Scale-up from bench through production is essentially limited only by the capacity of the equipment available. The methods of the invention are particularly well suited for large scale concentration and desalting of nucleic acid samples, in contrast to other existing techniques, such as precipitation. Regardless of whether they are used for small-scale or large-scale production, however, the methods of the invention are rapid, highly reproducible, and give a high level of desalted recovery of nucleic acids. The present invention also avoids the required use

of a separate step involving cation exchange chromatography, precipitation, or other technique to introduce any desired non-volatile cation as a counterion for the nucleic acid.

Rejection of claims 1-20 under 35 USC 103

Claims 1-20 were rejected as being unpatentable over statements made in the specification. Specifically, the claims were rejected over statements made on page 2, first paragraph, page 12, lines 1-14, and page 14, last paragraph. These rejections are traversed as applied to the pending claims.

Obviousness under §103 must be determined by considering (1) the scope and content of the prior art, (2) the differences between the prior art and the patent claim, and (3) the level of ordinary skill in the pertinent art. *Graham v. John Deere Co.*, 383 U.S. 1, 148 U.S.P.Q. 459 (1966). In addition, objective evidence of non-obviousness, such as the commercial success of the claimed invention and any long felt but unmet need prior to the claimed invention, also must be considered in determining obviousness. *See, e.g., Specialty Composites v. Cabot Corp.*, 845 F.2d 981, 989 (Fed. Cir. 1988).

As to the first of the four factual inquiries under the *Graham* obviousness analysis, the scope and content of the prior art includes those materials defined by §102 that are in the same field as the claimed invention, as well as those that solve the same problem. The references referred to in the passages cited as rendering the invention obvious do in fact discuss nucleic acid purification, e.g. using anion exchange chromatography, but none of the references discusses methods of solving the same problem as the present invention, i.e. a method for more efficient concentration and desalting *following* this purification step.

Since the references offer guidance only as to the purification process and not the desalting and/or concentrating of the nucleic acid following chromatographic purification, they do not render the invention obvious under §103.

In assessing the second factor in the obviousness analysis, the differences between the prior art and the claims at issue, it is first necessary to determine the meaning, and thus the scope, of the claims, as set forth in the application. The currently pending claimed methods of the application recite a method of desalting and concentrating the oligonucleotides following purification by using a strongly hydrophobic matrix in the purification process. This allows the step of rinsing the bound oligonucleotide or monomer

with an unbuffered, aqueous solution, which desalts the oligonucleotide without the use of large quantitites of volatile, toxic organics.

Since the scope of the referenced prior art is concerned with a different end result (pure oligonucleotides) than is the end result of the methods of the present invention (desalted and concentrated pure oligonucleotides), the prior art does not render the invention obvious under §103.

The level of ordinary skill in the art, the third factual inquiry, is determined by evaluating the type of problems encountered in art; prior art solutions to those problems; rapidity with which innovations are made, sophistication of the technology; and educational level of active workers in the field. As mentioned above, the prior art methods that have been tried by those skilled in the art have significant limitations, even with the use of sophisticated techniques and expensive equipment. In addition, the level of skill in the art is quite high, and therefore if such a technique as the methods of the invention was indeed obvious it no doubt would have been discovered by those skilled in the art.

Objective indicia of non-obviousness, the last factor to be considered in the obviousness analysis, includes evidence that the claimed subject matter had gone undeveloped by others, despite a motivation for doing so. Thus, evidence of a long-felt need that had not been satisfied until the patentee's invention of the claimed subject matter provides some indication that the patentee's claims may not have been obvious, particularly if others had attempted to meet the need, but had failed. The need for improved methods was specifically stated at the IBC 2nd Annual Conference on Oligonucleotide Technologies, and the limitations of each available method spelled out. This makes it apparent that others in the field were attempting to find a method for desalting and concentrating oligonucleotides and/or monomers, and were met by only a limited success. Thus, the methods of the current invention, which are a distinct improvement over the other available methods, could not be obvious under §103.

CONCLUSION

The presently pending claims have been amended or added to more particularly point out and distinctly claim the subject matter of the invention. In addition, given the level of skill of those in the art and the great need in the art for methods of the claimed invention, the claims are not obvious under §103. Accordingly, Applicants respectfully request allowance of the currently pending claims.

The Commissioner is hereby authorized to charge any fees under 37 C.F.R. §§ 1.16 and 1.17 which may be required by this paper, or to credit any overpayment, to Deposit Account No. 50-0815.

Respectfully submitted,
BOZICEVIC, FIELD & FRANCIS LLP

Date: 6/17/99

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Pre-Conference Workshop — Monday, October 26, 1998

Patent Update and Licensing Strategies

Barry Datlof, Director of Patents & Licensing, American Red Cross

- Compare Oligo Company Patent Portfolios
- Inside the Patent and Trademark Office
- Review Legislative Proposals to Change US Patent Law

Pre-Conference Workshop — Monday, October 26, 1998

Patent Update and Licensing Strategies

8:00 *Main Conference and Workshop Registration, Coffee, Breakfast Pastries & Exhibit/Poster Set-Up*

9:00 **Patent Update and Licensing Strategies**

Barry Dallof, Director of Patents & Licensing, **American Red Cross**

- Compare Oligo Company Patent Portfolios
- Review Legislative Proposals to Change US Patent Law
- Inside the Patent and Trademark Office
- Finding Patent Information Online
- In-Licensing Contract and Negotiation Terms with Universities
- Strategic Alliances with Startups

This session will focus on the best practices for protecting intellectual property and commercializing those rights. Patent law and Patent and Trademark Office policies that have changed or been introduced will be analyzed. Want to know where to go for the latest online access to patent information? Negotiating with universities to in-license their technology can be successful if you know the wherefores and why's of their position. New startups need credibility; can your company lend it's backing in exchange for future rights?

12:00 *Close of Workshop*

12:00 - 2:00 *Buffet Luncheon*

MAIN CONFERENCE

1:00 *Main Conference Registration*

2:00 **A Convenient Synthesis of Oligonucleotides**

Yoshihiro Hayakawa, Ph.D., Professor, **Nagoya University,** *Japan*

A facile synthesis of oligonucleotides via the phosphoramidite approach using imidazolium traflate as a promoter has been developed. The new promoter allows highly O-selective phosphitylation of N-free nucleosides and the synthesis requires no nucleoside-based protection. This approach generally gives higher quality of products than the conventional base-protected method, which necessitates deprotection causing undesired cleavage of internucleotide linkages. The synthesis of oligonucleotides with modified backbone such as alkylphosphonate and phosphorothioate linkage.

2:30 **Light-Directed Synthesis of High-Density Oligonucleotide Probe Arrays**

Glenn H. McGall, Ph.D., Associate Director, Chemistry, **Affymetrix, Inc.**

High-density arrays of oligonucleotide probes are proving to be powerful tools for rapid, massively parallel analysis of genetic sequence information. This presentation will discuss technologies that we have developed for high-resolution photolithographic array fabrication, which integrate solid-phase oligonucleotide synthesis, organic photochemistry, and lithographic techniques adapted from the microelectronics industry.

3:00 **Analysis and Control of Synthetic Oligonucleotide - State-of-the-Art and Proven Strategies**

Mark Roach, Director, Quality Control, **Isis Pharmaceuticals, Inc.**

The characterization and control of synthetic phosphorothioate oligonucleotides presents challenges beyond that of small molecules typically seen in pharmaceutical drug development. In addition to routine analytical tools like HPLC and UV spectroscopy, the use of state-of-the-art analytical techniques, like capillary electrophoresis, to provide length-based separations and mass spectrometry for the determination of sequence information are needed to characterize and control the synthesis process and the release and stability testing of the drug substances and drug product for drug development. The use of these methods in a quality control environment will be discussed.

3:30 *Networking Refreshment Break and Exhibit/Poster Viewing*

4:00 **Current Trends in Oligonucleotide Synthesis and Purification Protocols — Cost-Effective Metric Ton Production**

Yogesh S. Sanghvi, Ph.D., Associate Director, Development Chemistry, **Isis Pharmaceuticals, Inc.**

Over a dozen antisense oligonucleotides are currently undergoing human clinical trials and with one of these reaching NDA stage, it is anticipated the market demand for these drugs may require over a metric ton of manufacturing per year. With this requirement in mind, this presentation will describe low-cost, large-scale synthesis and purification of antisense oligonucleotides for market. Furthermore, this presentation will discuss:

- Solution-Phase vs. Solid Phase Oligo Chemistries
- Introduction and Use of Environmentally Benign Reagents
- Novel Techniques of Oligonucleotide Purification Methods

4:30 **The Separation of Oligonucleotides by Ion Exchange and Reverse Phase — Phosphodiesters vs. Phoshorothioates**

Paul Kostel, MS, Senior Applications Chemist, **Vydac**

Oligonucleotides can be separated by ion exchange, ion in solvent or reverse phase depending on the molecular characteristics of the oligo and the purpose of the separation. Choice of separation methods will depend on:

- Trityl On vs. Trityl Off
- Phosphodiester vs. Phosphorothioate
- Analytical vs. Purification
- Research vs. Pharmaceutical Needs

5:00 *Open Floor Q & A*

5:30 **Ice-Breaker Cocktail Reception**

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